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Review

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Adult hepatoblastoma: Learning from children

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Summary

Hepatoblastoma is the most common malignant liver tumour in infants and young children. Its occurrence in the adult population is debated and has been questioned. The aim of this paper is to review the histological and clinical features of adult hepatoblastoma as described in the adult literature, and to compare the findings with those of paediatric hepatoblastoma. The developmental and molecular aspects of hepatoblastoma are reviewed and their potential contribution to diagnosis of adult hepatoblastoma discussed.

Case reports of adult hepatoblastoma identified by a PubMed search of the English, French, German, Italian, and Spanish literature through March 2011 were reviewed.

Forty-five cases of hepatoblastoma were collected. Age at presentation was variable. Survival was uniformly poor, except for the rare patients who presented with the relatively differentiated, foetal type. The common denominator between adult and paediatric cases is the occurrence of embryonal or immature aspect of the tumours. Whether the adult cases of hepatoblastoma represent blastemal tumours, stem cell tumours, or unusual differentiation patterns in otherwise more frequent adult liver tumours remains to be established. Adult tumours labelled as hepatoblastoma are characterised by malignant appearing mesenchymal components. Surgical management is the cornerstone of therapy in children and also appears to confer an improved prognosis in adults.

Whether adult hepatoblastoma exists, remains controversial. Indeed, several features described in adult cases are markedly different from hepatoblastoma as it is understood in children, and other differential diagnoses should also be entertained. Nonetheless, hepatoblastoma should be considered in adults presenting with primary liver tumours in the absence of pre-existing liver disease. Adult and paediatric patients with immature hepatoblastoma appear to have worse outcomes, and adults presenting with presumed hepatoblastoma have an overall poorer prognosis than children with hepatoblastoma. In all patients, surgery should be the treatment of choice, neoadjuvant chemotherapy is advisable.

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Introduction

Hepatoblastoma (HB) accounts for approximately 1% of all paediatric malignancies. Although rare, HB is the most common primary malignant hepatic tumour in children, with an annual incidence of 0.5–1.5 per million in the paediatric population. A majority of cases occur between the ages of 6 months and 3 years [1,2]. Although HB has been reported in adults, its occurrence in the adult population remains controversial. In the 2001 edition of the Armed Forces Institute of Pathology (AFIP) on Tumours of the Liver and Intrahepatic Bile Ducts, the authors declare that not one adult HB case had been recorded at the AFIP [2]. They postulate that the majority or all adult HB cases reported in the literature (approximately 40 at that time) were actually misdiagnosed hepatocellular carcinomas (HCC), combined HCC–cholangiocarcinomas, or carcinosarcomas. Even in paediatric malignant liver cell tumours, clear-cut distinction between HB and HCC may prove difficult, since molecular, histological, and clinical findings often overlap. These features are even more confusing in adults. We discuss the similarities and differences between paediatric and reported adult cases with respect to clinical presentation, treatment, outcome, and pathological findings.

In addition, we review what is known about the developmental aspects, the molecular characteristics and regulation of the different types of HB, how these relate to progenitor cells, and how these tools might be of use in identifying adult HB. Finally, we review surgical and medical management in children and offer recommendations as to how these should be considered in adults with HB features.

Materials and methods

This paper by no means intends to be an exhaustive review of paediatric HB. Instead, we review all 45 adult HB cases identified by a systematic PubMed search of the English, French, German, Italian, and Spanish literature through March 2011. The data were compared and contrasted to internationally recognised HB

Keywords: Malignant liver tumour; Adult hepatoblastoma; Histology; Treatment.
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Abbreviations: HB, hepatoblastoma; AFIP, Armed Forces Institute of Pathology; HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein; SIOP, International Society of Paediatric Oncology; PRETEXT, pre-treatment tumour extension; HPF, high power field.

criteria. Finally, in order to better characterise the outcome of adult HB, survival was assessed according to the Kaplan Meier method and group comparisons were performed using the log-rank test. Standard alpha level of 0.05 indicated statistical significance. Analyses were conducted using SPSS 15.0 (SPSS, Chicago, IL).

Clinical findings

Paediatric HB

Most HB affect children below the age of 3 years, and the median age at diagnosis is 1 year [3]. It classically arises within a healthy liver, unaffected by underlying disease. Children typically present with an asymptomatic abdominal mass, and diagnosis is thus often made late, when disease is already metastatic [4]. These tumours most commonly present within the right lobe of the liver [5]. The lung is the most frequent site for metastasis. Lymph node involvement is rare [4]. On occasion, HB presents with intra-abdominal bleeding secondary to a ruptured liver mass. Approximately 90% of patients have highly elevated serum alpha-fetoprotein (AFP) levels, which is both a sensitive diagnostic marker and a tool to monitor response to therapy [6,7]. However, the most poorly differentiated HBs (small cell undifferentiated for instance) often have normal AFP levels and are associated with poorer outcomes [6].

Adult HB

HB is rare in older children and exceedingly so in adults. The age span of adult patients presenting with presumed HB was 17–78 years (Fig. 1). Since 1958, 45 adult HB cases have been reported in the literature [8–49]. An epidemiological survey of fatal primary liver tumours in US residents less than 20 years of age, between 1979 and 1996, disclosed four histologically proven HB cases in the 15–19 year-old group [50]. These cases were not included in Table 1 since the authors considered their survey as paediatric.

Similar to what is seen in children, adult HB often presents with a large liver mass. Adult HBs affect the right or left liver lobes, and are very often uni-focal. AFP is often elevated, but may be normal, as seen in children (elevated in 18/45 reported cases, normal values in 8/45 cases, missing data in 19/45). Lymph node metastases were observed in a few cases [8,12,14,18,24,38], which is very atypical for HB as it is understood in children. This observation raises two points: (1) Does adult HB metastasize differently than what is understood in children? (2) Were these tumours improperly classified as HBs? Overall prognosis is poor, since most of the adult cases died shortly after surgical and/or medical treatment.

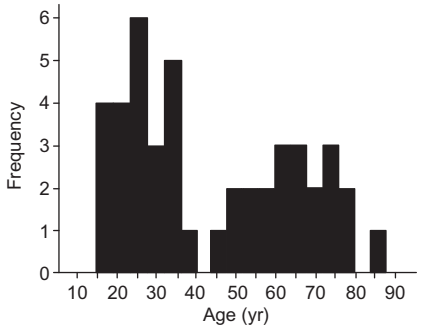

Fig. 1. Age distribution of adult hepatoblastoma. No rule can be found regarding age at manifestation.

Key Points 1

Clinical aspects of paediatric *vs.* adult hepatoblastoma

- Tumour characteristics:
  - Number of nodules are similar in children and adults
  - In children HB preferentially affects the right lobe, in adults both lobes are equally affected
- Metastatic behaviour is different between the two age groups:
  - Paediatric patients may display pulmonary metastases at diagnosis
  - Adult patients may have lymph node and visceral metastases (including lung)

Pathological findings in HB

Gross findings

Histology is central to the diagnosis of HB, but first we will briefly review the gross characteristics.

Paediatric HB

The gross findings in the 35 HB case series reported by Ishak and Glunz vary according to the subtype [51]. Half of the tumours considered were encapsulated. A large majority showed a bulging nodular or lobulated cut surface. In the mixed epithelial and mesenchymal HBs, a lobulated appearance is described, with intervening white collagen bands, and areas of necrosis or haemorrhage. The tumour nodules were variegated, tan to yellow to greyish white, and a minority of cases showed bile-stained, green nodules. Six of the 19 reported mixed HBs had prominent vascular channels on the capsular or cut surface, and calcifications were noted in some of them. Most of the 16 epithelial HBs were nodular, uniform and solid. They appeared greyish to yellow or tan, with a minority displaying areas of haemorrhage or necrosis.

According to the AFIP fascicle, pure foetal HB is characterised by lobulated nodules whose colour often resembles normal liver parenchyma. Mixed epithelial and mesenchymal HB shows a more variegated appearance, with white and dense mesenchymal areas alternating with brown or green epithelial nodules [2]. Osteoid may be grossly apparent. Areas of necrosis and haemorrhage may be seen in both cases.

Adult HB

The gross findings in the described adult HBs are not different from those described in children. Some tumours are described as encapsulated or surrounded by a pseudocapsule, whereas others may display indistinct margins. The lesions are either single or multiple, and are frequently described as variegated, with areas of haemorrhage or necrosis. In mixed epithelial and

Table 1. Overview of the clinical findings of all published reports of cases recognised by the authors as adult hepatoblastoma (English, French, German, Italian, and Spanish literature).

Year [Ref.]	Age (yr)	Size	LS	LD	AFP	Metastasis	Medical treatment	Surgical treatment	Histological HB type	Follow-up	Alive
1958 [8]	43	7 to 10 cm in Ø	R + L	+	n.a.	diaphragm, LN, lung	symptomatic	-	mixed, >mesenchymal	6 mo	-
1969 [9]	78	19 x 6 x 13 cm	L	-	n.a.	-	-	explorative laparotomy with biopsy	mixed	4 wk	-
1974 [10]	19	19 cm in Ø	R	n.a.	no	-	-	right hepatic lobectomy	mixed	n.a.	n.a.
1976 [11]	34	10 x 12 cm	R	n.a.	n.a.	-	-	right lobectomy	mixed	n.a.	n.a.
1978 [12]	51	12 x 10 x 10 cm	R	n.a.	no	LN	-	-	mixed	death before surgery	-
1979 [13]	60	1 to 6 cm in Ø	R + L	+	↑↑	portal vein, rib	systemic chemotherapy	-	mixed	2 mo	-
1980 [14]	72	large tumor	R	+	n.a.	LN, peritoneum, lung	symptomatic	-	mixed	2 wk	-
1980 [15]	27	25 cm	R	-	n.a.	lung	-	wedge biopsy of the tumor	mixed	death immediately post-op.	-
1981 [16]	73	9 x 8 x 8 cm and ++ small nodules	R	+	n.a.	portal vein	-	laparotomy for biliary obstruction and biopsies	mixed, >mesenchymal	death immediately post-op.	-
1982 [17]	68	large tumor	R	n.a.	n.a.	n.a.	-	resection	mixed	n.a.	n.a.
1984 [18]	58	5 x 3 x 6 cm	R	n.a.	n.a.	LN	-	atypical right hepatectomy	epithelial	5 mo	-
1987 [19]	25	20 x 10 cm	R	n.a.	n.a.	n.a.	-	atypical resection after rupture	epithelial	2 wk	-
1987 [20]	53	15 cm in Ø	R	n.a.	n.a.	-	-	right hepatectomy	mixed	1 yr	+
1989 [21]	22	7 x 6 x 6 cm	L	-	↑↑	pancreatic head	chemotherapy	left lobectomy + pancreaticoduodenectomy	epithelial	9 mo	-
1989 [22]	24	19 x 16 x 19 cm	R	n.a.	n.a.	-	-	right lobectomy	mixed	n.a.	n.a.
1989 [23]	18	12 cm in Ø	R	n.a.	↑↑	ovaries	systemic chemotherapy	resection of ovaries	epithelial	9 mo	-
1990 [24]	66	1 to 12 cm in diameter	R	+	n.a.	LN	-	-	mixed	11 d	-
1990 [25]	82	7 cm at initial diagnosis	R	+	↑	portal vein, from hepatic vein into atrium	arterial embolization, chemoembolization	-	mixed	5 mo	-
1992 [26]	35	n.a.	n.a.	-	n.a.	n.a.	n.a.	n.a.	epithelial (pure foetal)	n.a.	n.a.
1992 [26]	73	18 x 18 x 10 cm	R	+	n.a.	n.a.	n.a.	n.a.	mixed, >mesenchymal	n.a.	n.a.
1994 [27]	25	1 to 20 cm in Ø	R + L	-	no	-	-	explorative laparotomy with only biopsy	epithelial	1 mo	-
1994 [27]	19	1 to 7 cm in Ø	R + L	-	no	lung	-	percutaneous biopsies → hemorrhage	epithelial	1 d	-
1995 [28]	24	6 x 5 x 3 cm	R	-	n.a.	n.a.	arterial embolization	extended right lobectomy	mixed	16 mo	-
1995 [29]	28	diffuse, involving liver + bile ducts	R + L	+	↑↑	n.a.	-	palliative surgery	mixed	4 wk	-
1995 [30]	22	14 cm in Ø	n.a.	-	↑	n.a.	-	extensive hepatectomy	epithelial (pure foetal)	38 mo	+
1996 [31]	21	large tumor	R	-	n.a.	n.a.	recurrences treated with chemo- and alcoholic embolizations, systemic chemotherapy	right trisegmentectomy	epithelial	151 mo	+
1996 [31]	39	8 cm in Ø	L	+	n.a.	n.a.	-	liver resection and Billroth II	mixed	15 mo	-
1996 [32]	61	6 cm in Ø	L	-	↑↑	-	arterial embolizations	left lobectomy	mixed	n.a.	n.a.
1997 [33]	67	10 cm in Ø	R	-	no	-	-	resection of segments IV, V and VI	mixed	2 wk	-

(*continued on next page*)

Table 1. (continued).

Year [Ref.]	Age (yr)	Size	LS	LD	AFP x1000	Metastasis	Medical treatment	Surgical treatment	Histological HB type	Follow-up	Alive
1997 [34]	51	10 x 8 x 14 cm	L	+	↑↑	-	-	left lateral segmentectomy	mixed	2 mo	-
1997 [35]	44	18 x 13 cm	n.a.	-	no	direct extension to diaphragm	-	extended right hepatectomy	epithelial	5 mo	-
1999 [36]	27	1 to 10 cm in Ø	R + L	+	↑↑	lung	systemic chemotherapy	-	epithelial	1 mo	-
1999 [37]	47	1 to 2 cm in Ø	R + L	-	30,000	adrenal	-	-	mixed	some weeks	-
2001 [38]	23	15 x 12 x 9 cm	L	n.a.	n.a.	LN	systemic chemotherapy	left lobectomy	epithelial	n.a.	
2001 [39]	18	11 x 10 x 80 cm	R	+	1548,000	portal vein	-	right lobectomy	mixed	12 mo	+
2004 [40]	20	4.5 to 18 cm in Ø	R + L	-	↑↑	peritoneum	arterial embolizations for tumor rupture	left trisegmentectomy including parts of the diaphragm	epithelial	2 mo	-
2005 [41]	78	23 cm in Ø	R	+	↑↑	-	-	left lateral hepatectomy	mixed	10 wk	-
2005 [42]	52	11 x 19 x 22 cm in the left lobe and 3 cm in segment VIII	L	+	no	-	radiofrequency for right-sided lesion	left lateral hepatectomy	epithelial	10 d	n.a.
2006 [43]	19	14 cm in Ø	R	-	no	n.a.	systemic chemotherapy	right trisegmentectomy	mixed	6 mo	-
2007 [44]	34	1 x 11 x 9 cm	R	+	↑↑	-	-	right lobectomy	mixed	3 mo	-
2007 [45]	17	multiple lesions involving both lobes	n.a.	-	↑↑	-	chemotherapy	surgery	epithelial	n.a.	n.a.
2009 [46]	54	3 and 6 cm in Ø	R	+	↑	-	chemoembolization for recurrence	right lateral sectionectomy/right hepatectomy	mixed	31 mo	+
2010 [47]	25	25 x 15 x 18 cm	n.a.	-	↑↑	lung	systemic chemotherapy and chemoembolization	left trisegmentectomy	epithelial	4 yr	n.a.
2010 [48]	30	23 x 14 x 13 cm	R	-	↑	-	-	right trisegmentectomy	mixed	n.a.	n.a.
2011 [49]	33	19 x 15 x 14 cm	L	-	↑↑	direct extension to stomach; right lobe of the liver; lung	systemic chemotherapy and chemoembolization	left hepatectomy	mixed	1 yr	-

HB, hepatoblastoma; AFP, alpha-fetoprotein; no, normal; ↑, moderately elevated; ↑↑, highly elevated; LN, lymph nodes; n.a., not available, R, right; L, left; wk, weeks; mo; months; yr, years; LS, liver side; LD, liver disease; Ø, diameter.

mesenchymal HBs, osteoid, bone, and cartilage may be grossly identified.

Histological criteria

Histological criteria of paediatric HB

The diagnosis of HB is mainly based on histology. In 1967, Ishak and Glunz proposed two HB subtypes: (1) epithelial, (2) mixed epithelial and mesenchymal. Prior to this description, HB may have been unrecognised or labelled differently [51]. A more aggressive macrotrabecular pattern, and the small cell undifferentiated subtype were recognised later [52,53]. Not all of these conventionally accepted characteristics are found in adult lesions. In paediatrics, histology is commonly accepted to be of prognostic value, and as such plays a central role in determining therapeutic regimen.

Foetal and embryonal epithelial HB. The histological features of epithelial HB consist of irregular lobules delineated by collagen septa of varying thickness [51]. The septa contain vessels, some with a thick collagenous wall, and occasional lymphatics. The epithelial cells are subdivided in "foetal-type and embryonal-type cells" [2].

Foetal cells closely resemble the developing foetal liver, and are arranged in irregular 2-cell thick plates (Fig. 2A). They are smaller and more irregular than normal hepatocytes, with a moderately abundant acidophilic cytoplasm, and a round to oval, slightly irregular and basophilic nucleus. Pale cells, rich in glycogen, alternate in a typical pattern with darker cells. Steatosis, and intracytoplasmic or intracanalicular bile plugs may also be present. Extramedullary haematopoiesis is frequent.

Embryonal cells appear far less differentiated: they are small, elongated and poorly cohesive (Fig. 2B). They are arranged in sheets or ribbons, focally organising into acinar or papillary structures, or pseudorosettes. Embryonal cells are dark cells, with poorly defined contours. Cytoplasm is scant and amphophilic. The round to oval nucleus is hyperchromatic and contains a large nucleolus. Mitoses are much more frequent in the embryonal

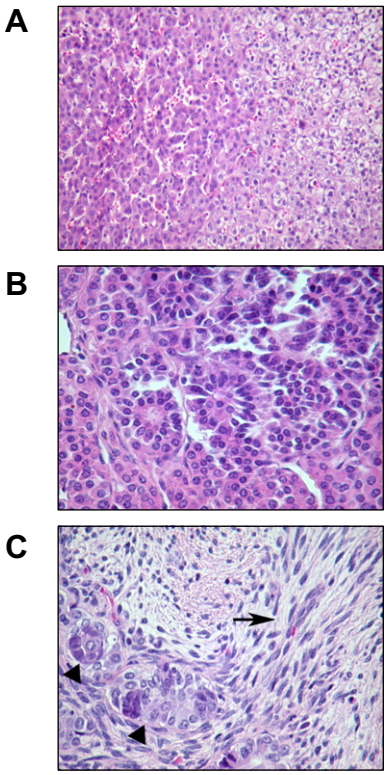

Fig. 2. Histological features of different types of paediatric hepatoblastoma (HB). (A) Foetal HB. Foetal cells resemble the developing foetal liver, and are arranged in irregular 2-cell thick plates. A characteristic light and dark pattern is imparted by variable cytoplasmic amounts of glycogen (haematoxylin & eosin stain (H&E); original magnification 100×). (B) Embryonal HB. Embryonal cells appear less differentiated, small, elongated and poorly cohesive, forming pseudorosettes (H&E, 200×). (C) Mixed (epithelial and mesenchymal) HB. In addition to the epithelial elements (arrowheads), primitive mesenchyme consists of spindle–shaped cells with plump elongated nuclei, in a parallel orientation (arrow) (H&E, 200×).

areas than in the foetal-type areas. Unlike in the foetal type, the embryonal type is characterised by the absence of glycogen, bile pigment, or steatosis.

Mixed epithelial and mesenchymal HB and teratoid features. The presence of mesodermal derivatives is characteristic of mixed, epithelial and mesenchymal HB. (Fig. 2C) [51]. These mesenchymal elements consist of a proliferation of primitive-appearing mesenchymal spindle-shaped cells, intimately admixed with the epithelial elements in a highly cellular pattern. Cytoplasm is more abundant than that of mature fibroblasts, and the nucleus is elongated, and plump. These cells blend progressively with areas of less intense cellular mesenchymal proliferation, and with the relatively acellular, fibrous septa. Osteoid is present in a majority of cases, either within the primitive mesenchyme, near the fibrous septa or pseudocapsule, or admixed within the epithelial elements. Osteoid foci contain cells morphologically identical to osteoblasts. Occasionally, squamous foci and a variety of mesenchymal and epidermal derived tissues are visible, which are considered teratoid elements [54,55]. Of note, neither cartilage nor rhabdomyoblasts were appreciated in the original description by Ishak and Glunz [54].

Macrotrabecular pattern. Gonzalez-Crussi *et al.* further described the more aggressive macrotrabecular pattern in HB, stressing the difficulties of classifying such tumours as HB or HCC [52]. They argued however that other areas in such tumours displayed a typical foetal pattern, thus lending support to a diagnosis of HB. The five patients described all died with progressive disease, some with unusual, skeletal metastases. The tumours displayed 10–20 or more cell thick trabeculae composed of foetal- or embryonal-appearing cells admixed with occasional cells larger than the normal uninvolved hepatocytes and anaplastic cells. In addition, there was marked vascular invasion within the tumours [52].

Small cell undifferentiated HB. The final HB subtype described in children is the small-cell undifferentiated pattern (SCU) previously called "anaplastic" [53]. This pattern is characterised by small, undifferentiated and poorly cohesive cells, with scant cytoplasm and hyperchromatic nuclei, initially described as "resembling neuroblastoma cells" [13]. Since 1989, small cell undifferentiated HB is the term used to describe tumours presenting with more than 50% of small-cell undifferentiated areas [56]. High mitotic rates and a possible primitive spindle cell component were reported in these tumours [56]. Some cases were associated with a foetal or an embryonal pattern [57].

Correlation between histology and outcome. Only HBs displaying a pure foetal histology and a low mitotic rate (<2 mitoses/10 high power fields, 400×) are defined as favourable histology, and have better survival [56]. All other subtypes are defined as unfavourable histology; in particular, SCU histology is associated with an adverse outcome [57].

In children with incompletely resected HB or with metastasis at initial diagnosis, identification of osteoid or chondroid foci, or of squamous differentiation has been associated with increased survival [56]. However, these elements had no influence on prognosis in completely resected HB. Since paediatric HBs with mesenchymal components have not been shown to behave more aggressively than other subtypes, they are not mistaken for sarcomas, unlike what might be a challenge in adult cases [52].

Histological criteria of adult HB

Whether HB exists in adults is controversial. As previously mentioned, most or all adult cases published were deemed misdiagnosed by the authors of the 2001 edition of the AFIP on Tumours of the Liver and Intrahepatic Bile Ducts [2]. We have not personally been confronted to adult cases of HB. This section will thus mostly be dedicated to a summary of the main findings in published adult HB cases, and to a discussion of the potential differential diagnoses in adults.

Underlying fibrosis or cirrhosis was identified in 11 of the 45 published HB adult cases [14,16,24–26,34,37,41,46,58]. An additional five patients had a history of viral hepatitis (A, B or C), but no reported fibrosis [13,31,36,39,42]. In contrast, childhood HB occurs almost always in patients with no underlying liver disease [59].

In adult HB, authors often underscore the malignant appearance of mesenchymal elements. Such areas are described as reminiscent of fibrosarcoma, osteosarcoma, chondrosarcoma, angiosarcoma, or rhabdomyosarcoma [9,13–15,17,24,26,32,34,41,49]. The latter deserves particular mention, since rhabdomyoblasts were not observed in the two large paediatric series

[52,53], although they were described sporadically in another series [60]. Identification of rhabdomyoblastic differentiation should therefore prompt careful evaluation of all tumour features, and consideration of differential diagnoses, such as teratoma [52]. Conversely, small undifferentiated cells are not pathognomonic of HB. For example, scattered clusters of highly undifferentiated oval or round cells, with scant cytoplasm in the epithelial component of a rhabdomyosarcoma-like liver tumour, were not considered diagnostic of HB in a 70-year old patient [61].

Differential diagnosis of adult HB

Hepatocellular carcinoma, and combined hepatocellular–cholangiocarcinoma with stem cell features

The main differential diagnosis of HB is HCC. The challenge is to distinguish HB from HCC which often show significant gross and histological overlap. Both tumours can present with a macrotrabecular pattern or poorly differentiated characteristics. Moreover, immunohistochemistry is of limited value in distinguishing between HCC and HB. To further complicate matters, both mixed HB and HCC features can exist within a same tumour [62]. Furthermore, the sequential development of HB and HCC in the same patient has been reported [46,63]. Finally, chemotherapy may result in cytologic and architectural modifications that mimic HCC, with resulting increases in both tumour cell size and nuclear anaplasia [64]. When present, mesenchymal elements are a key feature of paediatric HB. In contrast, in adult liver tumours, the presence of spindle-cells is not conclusive, since they can also be seen in HCC and in sarcomatous liver tumours. Table 2 summarises the main histological criteria to distinguish HB from HCC. Extramedullary haematopoiesis is a useful criterion in the diagnosis of HB, but may also be observed in a small subset (5%) of HCC cases. Bile production is more rarely seen in HB than in HCC [2]. Paediatric HB rarely occurs in the setting of underlying liver disease while 25% (11/45) of published HB adult cases showed underlying fibrosis or cirrhosis [13,14,16,24–26,34,37,41,46].

Patients with combined hepatocellular–cholangiocarcinoma are thought to have worse clinical outcome than patients with pure HCC [65]. Some tumours further display stem cell features, with clusters of small cells with high nucleocytoplasmic ratio, and hyperchromatic nuclei. The immunophenotype recapitulates that of stem or progenitor cells, with reactivity to the progenitor cell/ductular markers cytokeratins 7 and 19, neural cell adhesion molecule (NCAM1/CD56), KIT (CD117), epithelial cell adhesion molecule (EpCAM), and the hepatic progenitor cell marker OV–6 [44,66–68]. It remains to be determined to what extent these features observed in patients with conflicting clinical outcome relate to the poorly or undifferentiated aspects described in some of the adult HBs.

Table 2. Histological clues and criteria distinguishing hepatoblastoma (HB) from classical hepatocellular carcinoma (HCC). HB and HCC may show significant architectural and morphological overlap; unambiguous distinction may prove difficult, especially in particular HB variants. Histological clues to diagnosis are provided and variants with major overlapping features described. Histologic HCC variants (fibrolamellar HCC, clear cell carcinoma, sarcomatoid HCC, sclerosing HCC) are not considered. N/C ratio, nuclear/cytoplasmic ratio; HPF, high power field.

	Hepatoblastoma		**Hepatocellular carcinoma (classical HCC)**	
Histological clues	• "Light and dark" pattern		• Underlying cirrhosis	
	• Extramedullary hematopoiesis		• Cytoplasmic inclusions, bile production	
	• Mesenchymally-derived tissue		• Bizarre nuclei, giant tumour cells	
	Foetal type HB	**Embryonal type HB**	**HCC (classical HCC)**	**HB-HCC overlapping patterns**
Architecture	Cords or thin plates, intervening sinusoids	Dense sheets, rosettes	Trabecular, acinar, scirrhous patterns	Trabecular architecture in macrotrabecular HB
Tumour cell trabeculae	Thinner	-	Larger	Large 10-20 cell-thick trabeculae in macrotrabecular HB
Tumour cell size	Smaller cell size	Small cells	Cells larger than normal hepatocytes	Small undifferentiated cells (SCU HB *vs.* undifferentiated characteristics in HCC)
Cell characteristics	Uniform small cuboidal cells resembling foetal liver	Irregular, angulated cells, resembling embryonal liver	Large polygonal cells (varies with tumour grade)	"HCC-like" cells in macrotrabecular HB
	Distinct cell membrane	Indistinct cell membrane	Distinct cell membrane	
	Uniform nuclei	Mild nuclear anisocytosis and hyperchromasia	Nuclear anisocytosis, hyperchromasia (vary with tumour grade)	
	Abundant clear, granular or smooth cytoplasm	Scant, more basophilic cytoplasm	Moderate amounts of eosinophilic cytoplasm	
	Low N/C ratio	High N/C ratio	Variable N/C ratio according to tumour grade	
Mitoses	Low mitotic rate	Frequent; bizarre mitoses uncommon	Frequent; bizarre mitoses	Higher mitotic activity in mitotically-active foetal HB (>2 mitoses/10 HPF)

Ossifying stromal–epithelial tumour/(calcifying) nested stromal epithelial tumour of the liver

Another important differential diagnosis is the rare, ossifying stromal–epithelial tumour. The three initial cases reported as ossifying stromal–epithelial tumours in the AFIP fascicle had been present since childhood, as a calcified liver mass [2]. Nomenclature is confusing: these rare tumours have also been called ossifying malignant mixed epithelial and stromal tumours of the liver [69], nested stromal epithelial tumours of the liver [70], desmoplastic nested spindle cell tumours of the liver [71], and calcifying nested stromal epithelial tumours of the liver [72]. Age range at presentation varies from 2 to 14 years [70], while age at the time of diagnosis is 2–33 years [72]. Tumours consist of mixed epithelial and stromal elements arranged in spindle and epithelioid cellular nests, surrounded by a concentric myofibroblastic proliferation. The stroma contains variable amounts of calcifications, osteoid, and bone [70,72]. The main difference with HB is immunohistochemistry: this rare tumour does not stain for HepPar1, AFP, and cytokeratin 7, whereas WT–1 reactivity is observed [70,72].

Transitional liver cell tumours

There is one report of aggressive malignant liver cell tumours displaying morphological aspects intermediate between HB and HCC which were labelled as transitional liver cell tumours (TLCT) [73]. This is a clinically relevant paediatric series because some of these tumours were identified as HB on pre-treatment diagnostic biopsy, whereas the post-treatment liver specimen displayed features more in keeping with HCC. Recently, as previously stressed, phenotypic modifications have been reported in post-treatment HB [64], with cellular maturation or modification to a HCC-like phenotype. Together, these reports highlight the difficulties in distinguishing between the two entities and should be considered in clinical management.

Recent molecular advances have allowed identification of different patterns of gene expression [74], and distinguishing between HB and HCC might soon rely on molecular techniques.

Key Points 2

Morphological aspects of paediatric *vs.* adult hepatoblastoma

- Gross findings are similar in paediatric and adult HB, but are not specific
- Histological differences between adult and pediatric HB include:
  - Sarcomatoid elements in adult HB. This finding may either represent a true difference between paediatric and adult cases, or identify cases belonging to other categories
  - Osteoid, chondroid and teratoid elements may be favourable prognostic factors in children, in particular settings
  - Small cell undifferentiated HB is recognized in a subset of pediatric HB, but has not been reported in adults. Identification of embryonal/undifferentiated cells in liver tumours is not diagnostic of HB
- Embryonal or undifferentiated cells indicate poor outcome in all adult liver tumours

Developmental and molecular aspects of HB

Early descriptions of HB highlighted its histological resemblance to the hepatoblast, commonly accepted as the bipotential precursor of both the hepatocyte and cholangiocyte lineages [51]. AFP expression by the tumour attests the expression of a 'foetal' programme. With the advent of molecular methods, a progenitor-cell origin has been convincingly demonstrated for HCC, joining the vast body of literature in support of a cancer stem cell hypothesis [75–77]. Several elements support a similar origin for HB: onset in infancy and childhood, association with genetic syndromes favouring overgrowth and tumour development [78–80], and frequent absence of underlying liver disease. In addition, histological subtypes appear to recapitulate foetal development to some extent and may include teratoid elements [81], suggesting a pluripotency of the tumour, or at the very least, the creation of a permissive environment for diverse cellular differentiation within the tumour itself. Finally, and perhaps most convincing, is the finding that the bipotential oval cell marker DLK1 has been shown to be upregulated in HB [82].

Several investigators have indeed used gene expression analysis to identify molecular signatures between subtypes. The different histological subtypes described above (foetal *vs.* embryonal, epithelial *vs.* mesenchymal, and small cell undifferentiated) offer an attractive avenue to explore genotype–phenotype correlations and possible embryonic origins. The common denominator of most of these studies has been the use of the foetal liver (usually murine) as a reference for liver development [83,84]. Most recently, Buendia and colleagues used a combination of gene expression profiles and array comparative genomic hybridization (CGH) analysis to show that foetal and embryonal subtypes mirror the molecular signature of early or late liver development [83]. This important study confirms a genetic and molecular origin to the long standing assumption that the more immature, embryonal phenotype leads to a more aggressive disease than the foetal type, commonly accepted as a sign of favourable outcomes [83].

Furthermore and most relevant to this review, a recent analysis using gene profiling of different adult HCCs showed that a subset of tumours clustered with mouse hepatoblasts around embryonic day 13–16 [75]. The subset of patients having this type had worse outcomes than non hepatoblast-like HCCs [75]. Taken together, these last two observations beg the question whether these tumours with molecular, foetal characteristics were not in fact adult HBs which might have warranted a different management than conventional HCC therapy.

The possibility of molecular overlap between HCC and HB is important when approaching an atypical adult hepatic epithelial tumour. Mixed HB and HCC phenotypes have been described within the same tumour [62], and the presence of both tumour types has been described in patients either in a synchronous or sequential fashion [46,63]. There can be significant histological resemblance between HB and HCC. Furthermore, as many as 28% of HCCs in one series stained positively for CK7 and/or CK19, compatible with a progenitor-cell origin. Interestingly, these CK19 positive tumours had a worse prognosis [85]. Additionally, developmental signalling pathways such as Wnt, Hh, and Notch which have all been shown to be important in HB pathogenesis [44,62,86–88], also play a more or less important role in the development and maintenance of HCC, which suggests

that there is at least some overlap in oncogenic programmes in these two tumours [86,89–91].

While it is tempting to consider that HB and HCC may share a common progenitor, this is far from clear. Indeed, the adult liver appears to contain multiple progenitor candidates ([92], reviewed in [88]) and it is true that chronic liver disease gives rise to HCC. The big difference between HCC and HB is that HB arises most often in a normal liver. Therefore, it is unclear whether indeed the same progenitor cell is at play. However, one might postulate that at least in some cases, there may be an overlap in the origin of the two tumours.

Key Points 3

Developmental aspects of hepatoblastoma and hepatocellular carcinoma

- Detailed molecular studies suggest that HB may derive from progenitor cells, akin to what is commonly accepted now for solid tumours, including HCC
- Molecular overlap and co-existence of HB and HCC in paediatric and adult patients support the emerging hypothesis that these two tumours may derive from a common progenitor cell
- Advances in the genetics of HB seem to support the long-standing hypothesis that its pathobiology in part recapitulates liver development
- Future studies will help
  - elucidate the molecular biology governing cell fate decisions thereby identifying potential therapeutic targets.
  - differentiate between HCC and HB

Therapeutic protocols and outcome

Therapy and outcome in paediatric HB

Overview

The International Childhood Liver Tumour Strategy Group (SIOPEL), a committee of medical specialists founded in 1988 under the umbrella of the International Society of Paediatric Oncology (SIOP), promotes basic and comprehensive clinical research on childhood malignant neoplasms of the liver, mainly HB and HCC. The ultimate goal of this study group is to ameliorate the prognosis and the quality of life of children affected by these rare neoplasms and to promote international cooperation (www.siopel.org).

Worldwide, there are two different strategies regarding the treatment of paediatric HB. The North American groups support immediate surgery for localised tumours [93,94], whereas Europe favours pre-operative chemotherapy in all cases, followed by surgery. In most cases and depending on risk factors and staging, post-operative chemotherapy is also recommended. In the following paragraphs, we summarise the current European strategy of risk-adapted therapy, as outlined by SIOPEL following European-wide research.

The prognosis for HB has dramatically improved since the introduction of effective, cisplatin-based chemotherapy in the 1980's. Five-year overall survival has improved from 25% to around 70% [95]. Alternating cycles of cisplatin, doxorubicin and even carboplatin are administered based on the risk-groups of HB patients (histological type, tumour extension, AFP secretion, etc.). The SIOPEL group is currently investigating the efficacy of a high-dose cisplatin regimen in high-risk patients and the efficacy of irinotecan in patients with recurrent disease [96]. These approaches might be part of future therapeutic strategies against advanced HB (www.siopel.org).

The SIOPEL established the PRETEXT (*pre*-treatment tumour *ext*ension) staging system, reflecting the number of liver sections with or without tumour (Fig. 3). The aim of the PRETEXT classification is to assess the feasibility of complete tumour resection prior to any treatment. This approach has shown reliable inter-observer reproducibility and an excellent prognostic value [97,98]. Its main limitation is the difficulty to distinguish between actual invasion of a liver segment or displacement of an anatomical border. This may lead to over-staging [99]. The SIOPEL studies have identified factors associated with lower survival in patients with HB: (1) tumour involving all four hepatic

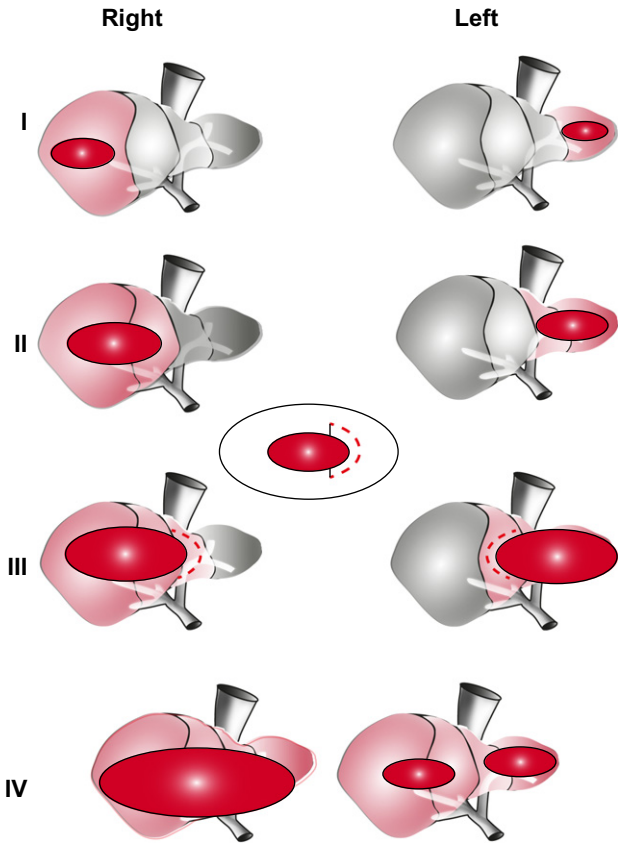

Fig. 3. PRETEXT (*pre*–treatment tumour *ext*ension) staging system (www.siopel.org). PRETEXT reflects the number of liver sections, which are free – or involved – of tumour: PRETEXT I: three adjoining liver sections free, one section involved; PRETEXT II: two adjoining sections free, two sections involved; PRETEXT III: two non-adjoining sections free or just one section free, in the latter case three sections involved; PRETEXT IV: no free section, all four sections involved.

sections (Fig. 3), (2) presence of distant metastasis, (3) tumour extension into the vena cava, all three hepatic veins or the main and/or both branches of the portal vein, (4) biopsy-proven extrahepatic intra-abdominal disease, (5) low serum AFP (<100 ng/ml), (6) tumour rupture at presentation [6,96]. Meyers *et al.* further exposed a histological factor to be prognostic: small undifferentiated histology showed to have worse prognosis [100].

Surgical strategies for paediatric HB

In Europe, surgery is usually performed *after* pre-operative chemotherapy. Complete tumour resection is the crucial step in curing HB [101]. Radical tumour resection can be achieved either by conventional hepatic surgery or orthotopic liver transplantation. As a general rule, PRETEXT I–III tumours are treated with partial hepatectomy, and PRETEXT IV or unifocal, centrally-located tumours with total hepatectomy, i.e. liver transplantation [101].

Large solitary PRETEXT IV HBs can be an exception to this principle as a local resection can become feasible after successful downstaging with pre-operative chemotherapy (thus avoiding liver transplantation). This may be the case when the anatomical border of a liver sector is compressed without true malignant invasion. On the other hand, unifocal, centrally-located HBs are more likely to be treated by liver transplantation when they involve the main hilar structures or main hepatic veins, as these structures would presumably not become tumour-free even after a good response to chemotherapy. Indeed, initial invasion of the portal or hepatic veins is not a definite contraindication to liver transplantation [102,103]. Yet, a review including the worldwide experience with HB has shown that such venous invasions are associated with significantly lower survival after liver transplantation: long-term survival was 54% if macroscopic venous invasion was present *vs.* 78% if there was no invasion [95].

Of note, children with multifocal PRETEXT IV tumours in whom tumour nodules respond to pre-operative chemotherapy should also benefit from primary liver transplantation (provided that all lesions cannot be removed by partial liver resections). This principle is guided by the high risk of recurrence from small non-detected viable HB cell remnant after chemotherapy. The sites of all currently and previously visible HB lesions should be excised [104].

Lung metastases are not an absolute contraindication to liver resection or even liver transplantation. All pulmonary metastases should be removed first (wedge resection with wide margins) and the primary tumour subsequently resected – either by partial hepatectomy or by liver transplantation [105]. Some data even support that liver transplantation is a reasonable option if lung metastases have been eradicated by chemotherapy [95].

The rare absolute contraindications to liver transplantation are (1) the persistence of one or more viable extrahepatic tumour deposits not amenable to surgical excision; and (2) non-response to pre-operative chemotherapy, because of the high likelihood of systemic dissemination of the tumour [95].

In selected patients with HB, special hepatic resection techniques may be used by experienced liver surgeons [106]. Exceptionally, if the tumour is adjacent to major vessels, they may be resected and reconstructed. Similarly, pre-operative hepatic artery chemoembolization may be considered [107]. Even tumour encasement or ingrowth into the retrohepatic vena cava may not preclude a radical excision, since the vein can be resected en bloc and replaced under total vascular exclusion of the liver (which usually is very well tolerated by children) [108,109]. Yet, difficult resections should be avoided. They carry a high probability of leaving residual tumour, especially with tumours adherent to major hepatic vessels. The significantly better survival rates obtained in patients who received a primary transplant after a good response to chemotherapy support the strategy of avoiding partial hepatectomies when radical resections seem difficult and unlikely. Excellent results have been reported with primary liver transplantation compared to those obtained by rescue transplantation: 6-year survival after primary transplantation has been shown to be 82% *vs.* 30% for patients with rescue transplantation after primary partial liver resection [95]. Consequently, when

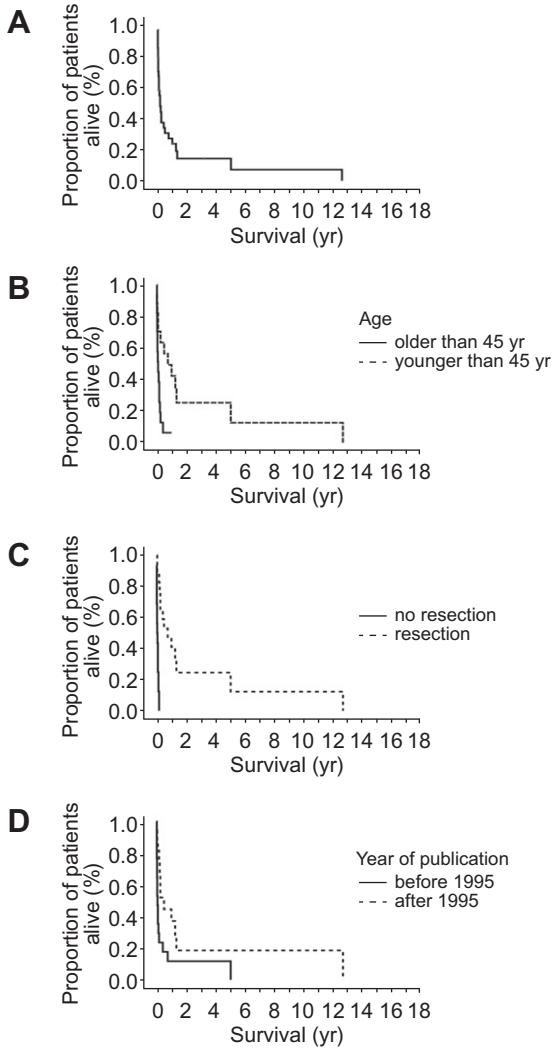

Fig. 4. Survival of adult hepatoblastoma patients. (A) Overall survival of adult hepatoblastoma patients (n = 34). Median survival: 2 months (95% CI 0.09–3.91). One-year survival: 24%. (B) Survival of hepatoblastoma patients younger than and older than 45 years. One-year survival: 42 ± 13% if age ⩽45 (n = 17), 0% if age >45 ($p \leqslant 0.004$, n = 17). (C) Survival of surgically treated patients with adult hepatoblastoma. One-year survival: 41 ± 12% in patients with resection (n = 17), 0% in those with palliative management ($p \leqslant 0.001$, n = 16). (D) Survival of adult patients with reported hepatoblastoma before and after 1995. Patients treated after 1995 show a better survival curve ($p = 0.018$, n = 17 in both groups).

intra-hepatic recurrence is observed after a previous partial hepatectomy, the indication for rescue liver transplant remains controversial.

Therapy and outcome in adult HB

Based on the review of the literature, it is clear that there is no standardised management of adult HB. In all cases, surgery was the first-line approach, but pre-operative chemotherapy was not administered. Radical surgical excision appears to be the "gold standard". Based on paediatric experience, we suggest treating adults in the same way as children: start treatment with cisplatin-based pre-operative chemotherapy, followed by surgery. Multicentre efforts should focus on implementing standardised guidelines.

Outcome of adult HB is poor. Overall median survival in the reviewed adult population was 2 months (95% CI 0.09–3.91), 1-year survival being 24% (Fig. 4A). Similar to children, adult patients with foetal HB may have better survivals. However, only two such cases have been reported (only one including outcome data) and no meaningful statistical analysis could be conducted with this subgroup of HB. Younger patients demonstrated significantly better survivals (1-year survival: 42 ± 13% if age $\leqslant$45 and 0% if age >45, $p = 0.004$, Fig. 4B). Patients undergoing liver resection demonstrated improved survivals compared to those with biopsy and/or palliative treatment. One-year survival was 41 ± 12% in patients with resection and 0% in those with palliative management ($p \leqslant 0.001$, Fig. 4C). Chemotherapy had no impact on outcome. Patients reported since 1995 demonstrated better survivals than those reported prior to 1995, suggesting an improvement in the management of HB in adults ($p = 0.018$, Fig. 4D). Upon analysis of risk factors of the reported adult HB cases, the following variables did not impact on outcome: AFP-secretion ($p = 0.34$), size of largest tumour ($p = 0.81$) (univariate Cox analysis), as well as presence of metastasis ($p = 0.51$) (Kaplan Meier analysis).

Key Points 4

Suggested treatment strategies for paediatric *vs.* adult hepatoblastoma

- Application of paediatric HB protocols in adult HB may prove beneficial
- Surgery is the cornerstone of pediatric HB management and should be considered in adults
- Complete resection is mandatory

Conclusions

Whether adult hepatoblastoma exists, remains controversial since many features of published cases are not found in paediatric HB and vice versa, and differential diagnoses were felt to be possible. However, the diagnosis of HB should be considered in adults presenting with primary liver tumours in the absence of pre-existing liver disease. Patients with immature tumour characteristics have a poor prognosis. In all patients, surgery should be the treatment of choice, neoadjuvant chemotherapy is advisable. Collaborative efforts are necessary to confirm the existence of adult HB and further characterise these rare tumours. Molecular tools may soon help in making this diagnosis. Multicentre efforts will help in designing standardised protocols.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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